



DOCKET NO.: ISIS-4943

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Cook et al.

Confirmation No.: 3783

Serial No.: 09/996,263

Group Art Unit: 1635

Filing Date: November 28, 2001

Examiner: James Schultz

For: SUGAR MODIFIED OLIGONUCLEOTIDES

RECEIVED
OCT 20 2003
TECH CENTER 1600/2900

(handwritten)
10/28/03
JDS

DECLARATION OF DR. SIDNEY M. HECHT
PURSUANT TO 37 CFR § 1.132

I, Dr. Sidney M. Hecht, declare that:

1. All statements herein made of my knowledge are true and statements made on information or belief are believed to be true. The Exhibits attached hereto are incorporated by reference.

2. I am the J.W. Mallet Professor of Chemistry and Professor of Biology at the University of Virginia. I serve as a member of the Scientific Advisory Boards of Xenogen, Galileo Laboratories and Palumed, and as a consultant for Isis Pharmaceuticals. I am President of Pinnacle Pharmaceuticals and a member of the Board of Directors. I also am a member of the Board of Directors of Orchid BioSciences. I serve as an Associate Editor of the *Journal of the American Chemical Society* and sit on the Editorial Advisory Boards of *Anti-Cancer Drug Design*, *Bioconjugate Chemistry* and *Current Medicinal Chemistry-Anticancer Agents*.

From 1981 to 1987 I held concurrent appointments at Smith Kline & French Laboratories, first as Vice President Preclinical R&D, then as Vice President Chemical R&D. I have been an Alfred P. Sloan Fellow and a John Simon Guggenheim Fellow at the Max Planck Institut für Experimentelle Medizin at Göttingen. In 1991 I served as a Professor Associé at the Muséum National d'Histoire Naturelle in Paris and Gastprofessor at the Eidgenössische Technische Hochschule in Zürich; I studied at the Museum again for six months during 2000. I have held numerous lectureships at other universities. I received the 1996 Cope Scholar Award of the American Chemical Society and was selected as Virginia's Outstanding Scientist for 1996. More recently I received the 1998 Research Achievement Award of the American Society of Pharmacognosy.

A copy of my curriculum vitae is attached hereto as Exhibit A.

3. I have read and am familiar with the contents of the above-referenced patent application entitled "Sugar Modified Oligonucleotides" (Exhibit B hereto), which I understand to have been filed with the United States Patent and Trademark Office on November 28, 2001 and is identified by patent application serial number 09/996,263 (the "263 application").

4. I have also read and am familiar with patent application serial no. 07/853,932, filed March 5, 1992, which issued as United States Patent No. 5,670,633 (Exhibit C hereto) (hereinafter the "633 patent"). I also have reviewed the pending claims (claims 8-13, Exhibit D hereto).

5. I consider myself to be a person having skill in the field to which claims 8 to 13 pertain. I also consider myself to be a person who had skill in this field in 2001 (when the

263 application was filed) as well as in 1992 (when the application that led to the 633 patent was filed). Each of claims 8 to 13 is directed to a mixed sequence oligonucleotide or oligonucleotide analog including more than one different 2'-modified 2'-deoxyfuranosyl moiety. The 2'-substituents are chosen from halo, azido, amino, alkoxy, thioalkoxy, alkylamino, and alkyl.

6. I have read the Office Actions dated March 26, 2003 and August 12, 2003. I understand that the Patent Office has asserted that claims 8 to 13 contain subject matter that is not described in the 263 application in such a way as to reasonably convey to those skilled in the art that the inventors had possession of the claimed subject matter. Specifically, the Patent Office asserts that the 263 application does not provide written support for oligonucleotides that comprise more than one different 2'-modification selected from halo, azido, amino, alkoxy, thioalkoxy, alkylamino, and alkyl.

7. I have read the 263 patent application and note that at page 10, line 30 to page 11, line 4, the application describes the following 2'-modified oligonucleotides:

"Oligonucleotides particularly suited for the practice of one or more embodiments of the present invention comprise 2'-sugar modified oligonucleotides wherein one or more of the 2'-deoxy ribofuranosyl moieties of the nucleoside is modified with a halo, alkoxy, aminoalkoxy, alkyl, azido, or amino group. For example, the substitutions which may occur include F, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, SMe, SO₂Me, ONO₂, NO₂, NH₃, NH₂, NH-alkyl, OCH₃=CH₂ and OCCH. In each of these, alkyl is a straight or branched chain of C₁ to C₂₀, having unsaturation within the carbon chain. A preferred alkyl group is C₁-C₉ alkyl. A further preferred alkyl group is C₅ - C₂₀ alkyl."

8. The 263 application also provides an example of an oligonucleotide having both 2'-methylthio *and* 2'-O-methyl substituents. Example 13 (page 64, lines 1-17) discloses the preparation of oligonucleotides having more than one different 2'-modification. Specifically,

the Example discloses oligonucleotides having 2'-deoxy-2'-methylthio substituents in certain positions and each of the nucleotides at the remaining positions have a 2'-O-methyl substituent. "Thus, all the nucleotides within the oligonucleotide included a substituent group thereon, either a 2'-deoxy-2'-methylthio substituent or a 2'-O-methyl substituent." (See page 64, lines 5-8).

9. I do not agree with the Patent Office that the subject matter defined by claims 8 to 13 is not described in the 263 application. It is apparent to me, upon review of the 263 application, that it describes the claimed subject matter, and that its inventors invented -- and thus had possession of -- this subject matter. The oligonucleotide of Example 13 having more than one different 2'-modification coupled with the disclosure of other possible 2'- modifications as set forth on page 10 leads me to conclude that those of skill in the art would acknowledge the inventors had possession of the claimed subject matter in the 263 application. The specification and examples taken as a whole teach one skilled in the art to produce an oligonucleotide with more than one different 2'-modification and that the choices from among which the 2'-modifications can be made include halo, azido, amino, alkoxy, thioalkoxy, alkylamino, and alkyl.

10. Having read the Office Actions, I understand that the Patent Office also asserts that the specification of the 633 patent does not disclose any single oligonucleotide that comprises two or more different modifications on the same oligonucleotide. In view of the alleged absence of such a teaching, the Patent Office asserts that the 633 patent does not provide adequate written description support for the full breadth and scope of the claimed oligonucleotides.

11. I have read the 633 patent and note that at Col. 7, lines 43-54 the application discloses the following 2'-modified oligonucleotides:

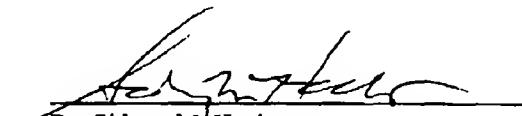
"Oligonucleotide analogs particularly suited for the practice of one or more embodiments of the present invention comprise 2'-sugar modified oligonucleotides wherein one or more of the 2'-deoxy ribofuranosyl moieties of the nucleoside is modified with a hydrogen or hydroxyl, halo, azido, amino, alkoxy, thioalkoxy, alkylamino, or alkyl group. For example, the substitutions which may occur include H, OH, F, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, SOMe, SO₂Me, ONO₂, NO₂, N₃, NH₂, NH-alkyl, OCH=CH₂, OCCH where alkyl is straight or branched chain of C₁ to C₁₂ with unsaturation within the carbon chain such as allyloxy."

12. The 633 patent at Col. 28, lines 35-43, also discloses an example of oligonucleotides having more than one different 2'-modification. Specifically, Example 13 discloses an oligonucleotide having both 2'-methylthio *and* 2'-O-methyl substituents. The Example discloses oligonucleotides having 2'-deoxy-2'-methylthio substituents in certain positions and each of the nucleotides at the remaining positions have a 2'-O-methyl substituent. "Thus, all the nucleotides within the oligonucleotide included a substituent group thereon, either a 2'-deoxy-2'-methylthio substituent or a 2'-O-methyl substituent." (Col. 28, lines 40-43).

13. I am of the opinion that the disclosure in the 633 patent of a specific oligonucleotide having more than one different 2'-modification (*i.e.*, Example 13 disclosing 2'-methylthio and 2'-O-methyl substituents) coupled with the disclosure of other possible 2'-modifications, such as halo, azido, amino, alkoxy, thioalkoxy, alkylamino, and alkyl (*see* Col. 7, lines 43-54), provides written description sufficient to support the full breadth and scope of the claimed oligonucleotides as of the 1992 filing date of the application that led to the 633 patent.

14. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/9/05


Dr. Sidney M. Hecht

Attachments

- Ex. A: Dr. Hecht's Curriculum vitae
- Ex. B: Application Serial No. 09/996,263
- Ex. C: United States Patent No. 5,670,633
- Ex. D: Pending claims 8 to 13